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<p>(21) International Application Number: PCT/US94/02911 (22) International Filing Date: 17 March 1994 (17.03.94) (30) Priority Data: 033,120 18 March 1993 (18.03.93) US (71) Applicant: MEDCLONE, INC. [US/US]; 2435 Military Avenue, Los Angeles, CA 90064 (US). (72) Inventors: FRENCH, Cynthia, K.; 14 Virgil Court, Irvine, CA 92715 (US). YAMAMOTO, Karen, K.; 12607 Mitchell Avenue, Los Angeles, CA 90066 (US). CHOW, Phoebe, M.; 321 West Grand Avenue #209, Alhambra, CA 91801 (US). ALIDO, Nemegias, T.; 2570 Highgate Court, Chino Hills, CA 91709 (US). (74) Agents: OLDENKAMP, David, J. et al.; Poms, Smith, Lande & Rose, Professional Corporation, 38th floor, 2029 Century Park East, Los Angeles, CA 90067 (US).</p>	<p>(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i></p>	
<p>(54) Title: ANTIGEN RELATED TO INFLAMMATORY DISEASES</p> <p>(57) Abstract</p> <p>An autoantigen identified as HP-8 which is related to systemic lupus erythematosus. The HP-8 antigen is expressed by a gene which was identified by immunoscreening of human placental cDNA GT11 expression library with the monoclonal antibody 3E10. The 3E10 antibody is a low-affinity anti-double-stranded DNA autoantibody derived from the MRL murine models for human systemic lupus erythematosus.</p>		

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ANTIGEN RELATED TO INFLAMMATORY DISEASES

BACKGROUND OF THE INVENTION1. Field of the Invention:

The present invention relates generally to connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE). More particularly, the present invention relates to antigens which are related to such diseases.

2. Description of Related Art:

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease which results in injury to the skin, joints, kidneys, nervous system and mucous membranes. SLE is not limited to these areas and can affect any organ of the body. SLE is an extremely debilitating diseases which is present in approximately one person in 800. The high frequency of SLE and its debilitating nature have resulted in intense study of this disease by the medical community.

In spite of the intense investigation the etiology of SLE is for the most part unknown. SLE is an autoimmune connective tissue disease which is characterized by the presence of a high level of autoantibodies. Patients with SLE typically have a wide variety of autoantibodies against nuclear and cytoplasmic cellular components. The antinuclear antibodies are known to be directed against a variety of materials including deoxyribonucleoprotein, DNA and histone. An exemplary antibody which has been associated with SLE is the 3E10 anti-DNA antibody (see Weisbart, et al., A CONSERVED ANTI-DNA ANTIBODY IDIOTYPE ASSOCIATED WITH NEPHRITIS IN MURINE AND HUMAN SYSTEMIC LUPUS ERYTHEMATOSUS, Journal of Immunology, Vol. 144, 2653-2658, No. 7, April 1990; U.S. Patent No. 4,812,397).

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The cause of SLE has not been established. However, factors that appear to contribute to the development of SLE include exposure to sunlight, genetic predisposition to the disease, certain drugs, viral and bacterial infection and hormonal influences. To
5 complicate matters further, the clinical manifestations of SLE are confusingly diverse. There is no specific cure for SLE since the underlying pathologies are not known. Accordingly, treatment involves supportive
10 measures employed to prevent or minimize acute relapses and provide relief from symptoms.

In view of the above, there is a continuing need to investigate the etiology of SLE and other inflammatory diseases in order to develop effective procedures for
15 prevention and treatment.

As part of this investigation, it is important that the various antigens, antibodies and other factors involved in SLE be isolated and identified so that their role in SLE can be established.

20

SUMMARY OF THE INVENTION

In accordance with the present invention, an antigen has been identified and isolated which is related to SLE. The antigen has been identified as HP-
25 8. The HP-8 antigen is expressed by a gene which was identified by immunoscreening of the human placental cDNA gt11 expression library with the 3E10 antibody mentioned above. The isolated cDNA gene sequence (insert size 154 bp) was found to hybridize to a 3.3 kb
30 and 1.2 kb mRNA transcript. It was found that the 3.3 kb transcript was expressed in brain, heart, placenta, lung, skeletal muscle and pancreatic tissues. The 1.2 kb transcript was found to be present in brain, heart, lung, skeletal muscle and kidney.

35 As a feature of the present invention, proteins which include the HP-8 antigen epitope are produced by

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recombinant means involving culturing of transformed micro-organisms which include the gene which codes on expression for the HP-8 antigen.

The HP-8 antigen is useful in mapping and
5 determining the genetic origin for expression of gene products in patients with SLE. In addition, the HP-8 antigen may be used in procedures for developing therapeutic rational drug designs to be used in treating SLE or other related connective tissue diseases such as
10 rheumatoid arthritis.

As another feature of the present invention, proteins and polypeptides which include the HP-8 antigen are used to raise antibodies in animals. The antibodies which are raised in response to the HP-8 antigen are
15 useful in the study and treatment of SLE.

The above-described and many other features and attendant advantages of the present invention will become better understood by reference to the following detailed description when taken in conjunction with the
20 accompanying drawings.

DETAILED DESCRIPTION OF THE INVENTION

The HP-8 antigen in accordance with the present invention is defined as a protein or polypeptide which
25 includes an epitope which is substantially homologous with the amino acid sequence set forth in SEQ ID NO: 2. The entire protein or polypeptide will have a molecular weight of less than 10 Kd based on mRNA size. Preferred proteins will have molecular weights on the order of 60
30 to 100 Kd, depending on glycosylation. To be considered substantially homologous, the amino acid sequence of the epitope of the protein or polypeptide must be 90 % homologous with the amino acid sequence set forth in SEQ ID NO: 2. Proteins and polypeptides which fall under
35 the definition of HP-8 must potentially bind 3E10 antibody, calcium, hydroxyapatite and collagen.

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HP-8 antigens in accordance with the present invention may be produced in accordance with any of the known processes for preparing polypeptides and proteins. It is preferred that the antigen be expressed in
5 prokaryotic, eukaryotic or insect viral cells by recombinant means. An exemplary procedure for producing HP-8 antigen is as follows:

A commercially available cDNA library was plated and screened according to manufacturers instructions.
10 cDNA library was a human placental cDNA GT11 expression library, Catalog No: HL-1075B (Clontech Laboratories, Palo Alto, CA). Large 150 mm LB soft agar plates were used to plate and screen the library with MAb 3E10. 0.6 ml of plating bacteria (Y1090) was incubated with a
15 proper dilution of lambda gt11 phage and absorbed to the cells at 37° C for 15 minutes. 7.5 ml of LB soft agar was added to the culture and quickly poured onto the plates and incubated at 42° C for 3.5 hours. Plates were removed and overlaid with a dry nitrocellulose
20 filter previously saturated in 10 mM Isopropyl-1-thio- β -D-galactoside (IPTG). The plates were incubated for an additional 3.5 hours at 37° C. Filters were removed and rinsed in 50 mM tris (pH 7.9), 150 mM NaCl, 0.05 % Tween (TBST) buffers. Filters were incubated with 10 ug/ml of
25 MAb in TBST buffer for 3 hours at room temperature. Following incubation filters were washed in three changes of Buffer A for 3 minutes each. Detection of bound antibody was done using the CLIK II Immunoscreening Kit (Clontech Laboratories, Palo Alto,
30 CA, Catalog number: K1004-2).

Detection of bound antibody used an alkaline phosphatase conjugate. Filters were incubated with goat-anti-mouse conjugate (2 ul) in 5 ml of buffer A for 30 minutes. Following incubation the filters were
35 washed 3 times with 50 ml of Buffer A (10 minutes each wash). An additional wash was done in Buffer C for 10

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minutes. Detection was performed by addition of 25 ul Nitro blue tetrazolium (NBT) (100 mg/ml) and 12 ul 5-Bromo-4-chloro-3-indolyl phosphate (BCIP) (100 mg/ml). Filters were incubated until signals became visible
5 under reduced illumination. The reaction was terminated by washing in 1 mM EDTA and positives selected. Six positives were identified in the screen and one was determined to be a true positive following secondary and tertiary rescreening using dilution cloning. The
10 positive, designated HP-8, was screened against normal human sera as a negative control indicating the validity of the 3E10 reactivity. Details of the preparation of the buffers are described in the Clontech Handbook (1992).

15 The lambda phage was grown up on plates according to protocols supplied from Clontech (pgs. 20-22, Clontech Protocol Handbook 1992). Isolated DNA was obtained and Eco RI digested using standard methods described in Maniatis, T. et al., (1989) Molecular
20 Cloning: A Laboratory Manual. 2nd Ed. (Cold Spring Harbor Laboratory Press; Plainview, NY). An insert of approximately 200 bases was resolved when electrophoresed in a 1% agarose gel in TBE. The insert was PCR amplified according to manufacturers
25 instructions and subcloned into pCR II. (Invitrogen, San Diego, CA, Catalog K2000-01). The subcloned fragment was retained as a hard copy template for subsequent expression cloning. Additional PCR amplification of insert was performed to generate
30 material for subcloning into pBLUESCRIPT for DNA sequencing. (Stratagene, La Jolla, CA, Catalog number: 212205).

The double-stranded pBLUESCRIPT pSKII+ plasmids containing the HP-8 specific clone fragment were grown
35 and DNA harvested using the Qiagen column purification system (Qiagen Corp., Chatsworth, CA, Catalog number:

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12162). T3 and T7 primers were used to sequence the cDNA. Procedures were followed using standard cycle sequencing conditions recommended by the manufacturers (ABI, Foster City, CA, Catalog number: 401384). The
5 nucleotide sequence and corresponding amino acid sequence are set forth in SEQ ID NO: 1 and SEQ ID NO: 2, respectively.

A multiple tissue northern blot was obtained from Clontech Laboratories, Palo Alto, California (Catalog
10 number: 7760-1) and hybridized to 32P labelled cDNA insert from HP-8. The probe was prepared according to manufacturers instructions (BRL, Gaithersburg, MD, Catalog number: 8187-SA) at high specific activity. Hybridization conditions were performed as described in
15 the Clontech handbook for Product number 7760-1. Washed filters were air dried and exposed to Kodak XR-5 x-ray film for 18 hours at -70°C.

The epitope of the HP-8 antigen (i.e. SEQ ID NO:2) is approximately 60-80 percent homologous with various
20 proteins and polypeptides which belong to the osteonectin family (see P.T. Russell et al., THE OSTEONECTIN FAMILY OF PROTEINS, J. Biochem., Vol. 20, No. 7, pp. 653-660, 1988). Specific examples of related osteonectin proteins are Osteonectin/BM401 SPARC and
25 SC1. These specific osteonectins are described in the following three references:

1. J.H. McVey et al., CHARACTERIZATION OF THE
30 MOUSE SPARC/OSTEONECTIN GENE, Jour. Biological Chem., Vol. 263, Issue of August 15, pp. 11111-11116, 1988;
2. J. Engel et al., CALCIUM BINDING DOMAINS AND
CALCIUM-INDUCED CONFORMATIONAL TRANSITION OF
SPARC/BM-40/OSTEONECTIN, AN EXTRACELLULAR
35 GLYCOPROTEIN EXPRESSED IN MINERALIZED AND
NONMINERALIZED TISSUE, Biochemistry, 1987, 26,

-7-

6958-6965; and

3. I.G. Johnston, et al., MOLECULAR CLONING OF
SC1: A PUTATIVE BRAIN EXTRACELLULAR MATRIX
GLYCOPROTEIN SHOWING PARTIAL SIMILARITY TO
OSTEONECTIN/BM40/SPARC, Neuron, Vol. 2, 165-
176, Jan. 1990.

DNA sequences which code on expression for the HP-8
antigen epitope may be inserted into appropriate
expression vectors for expression in prokaryotic
eukaryotic or insect viral cells. A wide variety of
expression vectors are available and may be used in
conventional procedures to transform competent host
cells for expression and isolation of the HP-8 antigen.
Methods for preparing gene sequences, inserting the
sequences into expression vectors, transforming
competent hosts and growing the host in culture for
production of products are disclosed in U.S. Patent Nos.
4,710,473; 4,711,843; and 4,713,339.

The HP-8 antigen can be used to generate
antibodies. The HP-8 antigen can be used in any of the
conventional procedures involving administering an
antigen to a host animal in order to raise antibodies.
The administration protocols, including dosage levels,
administration schedules and isolation and recovery of
antibodies from the host animal are all well known in
the art. The HP-8 antigen is used in the same manner as
any other antigen to elicit the production of antibodies
in a host animal.

The HP-8 antigen includes epitopes which bind 3E10
antibodies and therefore will be useful in investigating
the etiology of SLE. In addition, HP-8 will be useful
in developing therapeutic rational drug designs which
will be effective in treating SLE and other related
connective tissue diseases such as rheumatoid arthritis.
Further, the similarity of the HP-8 antigen epitope to

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osteonectin makes it amenable for use in the same manner as osteonectin.

All of the United States Patents, literature references and methodology handbooks set forth in this specification are hereby incorporated by reference.

Having thus described exemplary embodiments of the present invention, it will be understood by those skilled in the art that the above disclosures are exemplary only and that the present invention is not limited to the embodiments as disclosed herein, but is only limited by the following claims.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: French, Cynthia
Yamamoto, Karen
Chow, Phoebe
Alido, Nemy
- (ii) TITLE OF INVENTION: HP-8 AUTOANTIGEN
- (iii) NUMBER OF SEQUENCES: 2
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Poms, Smith, Lande & Rose
 - (B) STREET: 2029 Century Park East, 38th Floor
 - (C) CITY: Los Angeles
 - (D) STATE: CA
 - (E) COUNTRY: United States
 - (F) ZIP: 90067
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE:
 - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Oldenkamp, David J
 - (B) REGISTRATION NUMBER: 29421
 - (C) REFERENCE/DOCKET NUMBER: 95-110
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: 310-788-5000
 - (B) TELEFAX: 310-277-1297

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 132 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (vi) ORIGINAL SOURCE:

SUBSTITUTE SHEET

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(A) ORGANISM: Homo sapiens
(P) TISSUE TYPE: Placenta

(vii) IMMEDIATE SOURCE:
(B) CLONE: HP-8

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 17..148

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TGT	GTC	TGC	CAG	GAT	CCA	GTG	ACT	TGT	CCT	CCA	ACA	AAA	CCC	CTT	GAT	48
Cys	Val	Cys	Gln	Asp	Pro	Val	Thr	Cys	Pro	Pro	Thr	Lys	Pro	Leu	Asp	
1				5					10					15		
CAA	GTT	TGT	GGC	ACT	GAC	AAT	CAG	ACC	TAT	GCT	AGT	TCC	TGT	CAT	CTA	96
Gln	Val	Cys	Gly	Thr	Asp	Asn	Gln	Thr	Tyr	Ala	Ser	Ser	Cys	His	Leu	
			20					25					30			
TTC	GCT	ACT	AAA	TGC	AGA	CTG	GAG	GGG	ACC	AAA	AAG					132
Phe	Ala	Thr	Lys	Cys	Arg	Leu	Glu	Gly	Thr	Lys	Lys					
			35				40				44					

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Cys	Val	Cys	Gln	Asp	Pro	Val	Thr	Cys	Pro	Pro	Thr	Lys	Pro	Leu	Asp	
1				5					10					15		
Gln	Val	Cys	Gly	Thr	Asp	Asn	Gln	Thr	Tyr	Ala	Ser	Ser	Cys	His	Leu	
			20				25						30			
Phe	Ala	Thr	Lys	Cys	Arg	Leu	Glu	Gly	Thr	Lys	Lys					
			35				40				44					

SUBSTITUTE SHEET

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CLAIMSWhat is Claimed is:

1. A human antigen in substantially purified form, said antigen being identified as the HP-8 antigen.
2. A human antigen according to claim 1 wherein said antigen comprises the amino acid sequence set forth in SEQ ID NO:2.
3. A gene which codes on expression for the HP-8 antigen.
4. A gene according to claim 3 which comprises the nucleotide sequence set forth in SEQ ID NO:1.
5. A process for producing HP-8 antigen comprising the steps of:
 - providing a transformant microorganism, said microorganism including a recombinant vector comprising
 - 5 a gene which codes for the HP-8 antigen;
 - placing said transformant microorganism in a suitable nutrient medium;
 - culturing said transformant microorganism in said nutrient medium for a sufficient length of time to form
 - 10 HP-8 antigen;and
 - separating said HP-8 antigen from said nutrient medium.
6. A process for producing HP-8 antigen according to claim 5 wherein said gene codes for HP-8 antigen which comprises the amino acid sequence set forth in SEQ ID NO:2.
7. A process for producing HP-8 antigen according to claim 5 wherein said gene comprises the nucleotide

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sequence set forth in SEQ ID NO:1.

8. A method for producing antibodies comprising the steps of:

administering a sufficient amount of the HP-8 antigen to a mammal to illicit an immune response
5 wherein antibodies to the HP-8 antigen are produced; and
recovering said antibodies from said mammal.

9. A method for producing antibodies according to claim 8 wherein said antibodies include the 3E10 antibody.

10. A transformed microorganism which includes a recombinant vector comprising a gene which codes for the HP-8 antigen.

11. A transformed microorganism according to claim 10 wherein said gene codes for HP-8 antigen which comprises the amino acid sequence set forth in SEQ ID NO:2.

12. A transformed microorganism according to claim 10 wherein said gene comprises the nucleotide sequence set forth in SEQ ID NO:1.

13. An antigen made by a process comprising the steps of: providing a transformant microorganism, said microorganism including a recombinant vector comprising a gene which codes for the HP-8 antigen;

5 placing said transformant microorganism in a suitable nutrient medium;

culturing said transformant microorganism in said nutrient medium for a sufficient length of time to form HP-8 antigen; and

10 separating said HP-8 antigen from said nutrient

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medium.

14. An antigen made by a process according to claim 13 wherein said gene codes for HP-8 antigen which comprises the amino acid sequence set forth in SEQ ID NO:2.

15. An antigen made by a process according to claim 13 wherein said gene comprises the nucleotide sequence set forth in SEQ ID NO:1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/02911

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : Please See Extra Sheet.

US CL : 530/350, 387.1; 435/172.3, 69.3; 536/23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350, 387.1; 435/172.3, 69.3; 536, 23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,711,843 (CHANG) 08 December 1987, see entire document.	3-7, 10-15
Y	US, A, 4,713,339 (LEVINSON ET AL) 15 DECEMBER 1987, see entire document.	3-7, 10-15
Y	H. MANIATIS et al, "MOLECULAR CLONING, A LABORATORY MANUAL", published 1982 by MacGraw-Hill (N.Y.), pages 403-435, see entire document.	5-7, 10-15
Y	NEURON, Volume 2, issued 1990, Johnston, et al, "Molecular cloning of SC1: A putative brain extracellular matrix glycoprotein showing partial similarity to osteonectin/BM40/SPARC", pages 165-176, see entire document.	3-7, 10-15

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

09 MAY 1994

Date of mailing of the international search report

JUN 01 1994

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/02911

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BIOCHEMISTRY, Volume 26, issued 1987, Engel et al, "Calcium Binding Domains and Calcium-Induced Conformational Transition of SPARC/BM-40/Osteonectin, an Extracellular Glycoprotein Expressed in Mineralized and Nonmineralized Tissues", pages 6958-6965, see abstract, page 6959.	1, 2, 13-15
Y	Proc. Natl. Acad. Sci. USA, Volume 85, issued May 1988, Bolander et al, "Osteonectin cDNA sequence reveals potential binding regions for calcium and hydroxyapatite and shows homologies with both a basement membrane protein (SPARC) and a serine proteinase inhibitor (ovomucoid)", pages 2919-2923, see entire document.	1, 2, 13-15
Y	The Journal of Biological Chemistry, Volume 264, Number 9, issued 1989, Reeves et al, "Molecular cloning of cDNA encoding the p70 (Ku) lupus autoantigen", pages 5047-5052, see entire document.	1-4, 10-11, 14-15
Y	The Journal of Biological Chemistry, Volume 263, Number 23, issued 1988, McVey et al, "Characterization of the Mouse SPARC/Osteonectin Gene", pages 11111-11116, see entire document.	1-4, 14-15
Y	US, A, 4,812,397 (WEISBART) 14 March 1989, see entire document.	8-9
Y	J. Immunology, Volume 144, Number 7, issued 01 April 1990, Weisbart et al, "A Conserved Anti-DNA Antibody Idiotype Associated With Nephritis In Murine And Human Systemic Lupus Erythematosus", pages 2653-2658, see entire document.	8-9
Y	J. Immunology, Volume 110, Number 5, Mattioli et al, "Physical association of two nuclear antigens and mutual occurrence of their antibodies: The Relationship of the Sm and RNA protein (MO) systems in SLE sera", pages 1318-1324, see entire document.	8-9

INTERNATIONAL SEARCH REPORT

Int. .tional application No.
PCT/US94/02911

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (5):

C07K 3/12, 3/14, 3/28, 15/06, 15/12, 15/18, 17/02, 17/04; A61K 35/14; C12N 15/09, 15/10, 15/30; C12P 21/06;
C07H 17/08

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN, DIALOG, BIOSIS, CONFSCI, EMBASE, EDLINE, IG SUITE

Search terms: HP-8 antigen, autoimmune diseases, systemic lupus erythematosus (SLE), ribonucleoproteins